

Case Reports

**“Only that shall happen which has happened
Only that occurs which has occurred;
There is nothing new under the sun!”
Ecclesiastes 1,9**

The bit of wisdom from the Bible quoted above is applicable to case reports since in my experience and in that of many others, when one sees and recognizes a unique case he is apt to see a similar case in the future.

In this chapter, we will present some of the untoward reactions to hepatitis B vaccine that I have seen. They are representative of some of the reactions reported in the literature.

Case reports have been used for centuries as teaching tools to alert physicians as to what they might see in the future. This idea was advanced in the thirteenth century AD by a physician in Bologna, Italy, Dr. Taddeo Alderotti. He called collections of case reports, “Consilia”. It is in this frame of reference that the following case reports are being presented. These reports do not prove causation but when they are considered with the numerous similar case reports in the literature they may stimulate physicians to give pause when a patient presents with an adverse event that followed a hepatitis B vaccination.

A. Four cases of multiple sclerosis that occurred hepatitis B vaccination.

Case 1

This nurse was 34 years of age when she received hepatitis B vaccinations in November and December of 1984. The second day after the second vaccination she began to notice stiffness and pain in her cervical and high thoracic areas. This was followed by fatigue, dizziness and paresthesia in her right arm and hand. She also complained of numbness in the left facial area and scalp as well as a drooping eyelid. She consulted with a neurologist who considered multiple sclerosis and ordered a CT and an EMG, which were reported as normal. However, the symptoms persisted and the fatigue increased in severity. She then had a spinal tap that was normal. She suffered with these symptoms until July of 1985 when she was referred to me for consultation.

Due to my experience in finding multiple sclerosis that occurred after the swine influenza vaccination in 1976, I asked her whether she had any vaccinations. She responded that she had never had any difficulty before her hepatitis B vaccinations in November and December on 1984. However, she never made the connection between the vaccinations and her symptoms.

Her complaints in July of 1985 were of increasing weakness in her left arm, generalized migrating paresthesia, and extreme fatigue. On examination she was found to have demonstrable weakness of both her arms and hyperreflexia. At this time, her symptoms had progressed to the extent that because of weakness, fatigue, and paresthesia she had to discontinue nursing. Physical findings at that examination were absent abdominal reflexes, hyperactive reflexes elsewhere, and ataxia. Her repeat MRI in August 1985 was normal. At the suggestion of another consultant she was given 20 mg. of prednisone daily for a month. There was no response with her symptoms and findings remaining the same as they were in July 1985. The symptoms waxed and waned between July 1985 and June 1986.

An MRI in June 1986 was read as “findings consistent with demyelinating disease”. Starting in early 1987, the patient began to feel better. The MRI in June of 1987 was read as, “multiple sclerosis with evidence of resolution of some of the plaques since the prior scan.” An MRI in June of 1988 showed no change from that of 1987.

In November of 1988 the patient noted improvement and the only positive findings were bilateral weakness of both arms as evidenced by a Cybex examination. In early spring of 1989 she suffered an exacerbation with an increase in her arm weakness, increasing dizziness, and spasms in her neck muscles. By February of 1996, all her signs and symptoms had cleared and she felt normal.

The pharmaceutical company that was involved in a “failure to warn” lawsuit tacitly accepted some responsibility for her complications by settling the suit for a large sum of money, with of course, a secrecy clause.

Case 2

This nurse was 32 years old when she received her first hepatitis B vaccination in December 1988. She had never had any significant illnesses up to that time. She had no reaction to the first vaccination but several weeks after the second hepatitis B vaccination in early January of 1989, she developed pain in her left shoulder and forearm. Shortly thereafter, three fingers of her left hand became numb. After this, she developed pain in both shoulders that was associated with paresthesia.

The pain in the shoulders and paresthesia continued and was present when I first saw her in June of 1990. To these symptoms had been added bilateral paresthesia in both upper extremities and one leg. She had presented herself to me for consultation because a number of physicians had been unable to explain to her what was happening. Paresthesia, muscle weakness in her extremities, and hyperreflexia were the only physical findings. A spinal tap showed elevated protein and twenty mononuclear cells. An MRI showed an area of signal intensity that was read as, “could represent a focal area of demyelination”.

Due to my experience with the swine influenza vaccine and with Case 1, I immediately suspected that her demyelinating problems were related to her hepatitis B

vaccination. Neither the patient nor the physicians had made the connection between the hepatitis B vaccination and her clinical problems.

In August of 1990, she developed optic neuritis in her right eye. This responded to a course of oral prednisone.

In September of 1990, she was seen in consultation by a neurology professor of a major medical school. His conclusion was that she “had symptoms and laboratory data most consistent with a demyelinating process in the central nervous system”.

In 1992, because of exacerbation of arm pain, weakness, and fatigue she went for further consultation to the Mayo Clinic, in Rochester, Minnesota. Their report stated that she “has a clinically definite multiple sclerosis”.

Her symptoms plus extreme weakness caused her to resign her job as a critical care nurse and she was granted disability status.

I saw the patient last in November of 1997. Between 1992 and 1997 she had several exacerbations and remissions of her multiple sclerosis. She remained on permanent disability. On examination in November 1997, she had developed ataxia in addition to her other problems and was clinically fatigued.

It is of interest that in 1996, her case was reviewed by Dr. Jennifer Lloyd of the CDC and Dr. Gerald Fenichel, professor and chairman of the department of neurology at Vanderbilt University Medical School. They asked for her chart because apparently, they had been commissioned by the CDC to look into possible relationships between hepatitis B vaccination and demyelinating disease. In a letter to me Dr. Fenichel stated that he could not accept the patient’s case as one of multiple sclerosis. He stated this while he was in possession of the reports of the Mayo Clinic and of the professor of neurology and of the head of the department of neurology at the Medical College of Wisconsin. The results of the study by Drs. Fenichel and Lloyd have not been published or made available by the CDC.

This case report and the previous case report were submitted to the *JAMA*, *Wisconsin Medical Journal*, and the journal *Lancet* sequentially in 1989 and 1990. They were rejected for publication. One year later the *Lancet* published a paper by Dr. L. Herroelen of Belgium that confirmed the observation that multiple sclerosis can follow hepatitis B vaccination.

Case 3

This female social worker was 30 years old when she received a three-injection course of hepatitis B vaccine in 1987 and 1988. Several weeks after the first vaccination, she developed generalized muscle and joint pains. These continued in mild form, until after the third injection she developed extreme weakness and numb feet. The numbness and weakness continued. After a series of consultations that did not prove helpful, a

neurologist saw her in June of 1989. He made a diagnosis of multiple sclerosis. A second neurologist confirmed the diagnosis. He prescribed a course of corticosteroids to which there was little response.

When I examined her in November of 1992, she had hyperreflexia, bilateral numb feet, optic neuritis (confirmed by an ophthalmologist), and a staggering gait. I saw her again in November of 1995. By that time she was wheel chair bound, had bilateral temporal pallor, hyperactive reflexes, and bilateral positive Babinski reflexes. An MRI in November 1995, showed numerous lesions that were read as “classic for demyelinating plaques in multiple sclerosis”.

Case 4

This female United States Marshall had never been seriously ill until in August of 1993, when at age 34 she received a hepatitis B vaccination. A few hours after the vaccination she developed a flu-like syndrome with severe muscle aches. She had a fever of 101 degrees Fahrenheit and felt extremely weak. Her fever and the muscle aches and lassitude lasted one week. In September of 1993, she had her second hepatitis B vaccination. She developed a fever. She also had diarrhea, abdominal pain, nausea and anorexia. This lasted about a month. She was unable to sleep and suffered hallucinations. After her third vaccination in March of 1994, she almost immediately became ill with severe muscle weakness, fatigue, and localized weakness of her right hand.

During the period between 1994 and November 1999, when I saw her in consultation, she had remained chronically ill with multiple paresthesia, weakness and fatigue. This forced her, to retire from her occupation as a Federal Marshall. She had sought numerous consultations and had traditional “workups” by a wide coterie of specialists. She had seven hospitalizations. During one of these, it was necessary to do a sinus node ablation due to uncontrolled tachycardia.

On my examination in November 1999, she complained of fatigue, muscle weakness, and generalized paresthesia. Physical examination revealed ataxia, absent abdominal reflexes, and paresthesia over her arms and legs. In October of 1999 she had a MRI that was read as “certainly worrisome for multiple sclerosis”. I ordered a repeat MRI in August of 2000. This was read as “multiple foci of bilateral subcortical periventricular white matter hyperintensities. Demyelinating process would be considered”.

In November 2000, Copaxone was started with a dosage of 20 mg. to be given subcutaneously each day. I last saw the patient in February 2001. There has been improvement in all spheres of her condition. I talked to her in July 2001 and the improvement had continued.

B. Three cases of severe meningoencephalitis that followed hepatitis B vaccination.

Case 1

This nurse was 36 years old when she received a course of hepatitis B vaccination in June, July of 1988. In the fall of 1988 she developed a rash in her right axillary area that was raised red and circular. A dermatologist said it was dermatitis. Over the next few weeks, she developed intense pain in the right shoulder that spread down to the right arm, and caused tightness in the neck. She began to have discomfort going down both legs. She developed significantly intense headaches.

By January of 1989, the headaches became so severe that she had to give up her job. She saw several physicians between the fall of 1988 and January of 1989. They were unable to make a definitive diagnosis.

In late January of 1989, she was hospitalized and she slipped into a deep coma and could not be aroused. There were no localizing neurological signs. An MRI of her brain and spinal cord were read as normal. There were mononuclear cells in her spinal fluid. There were 79% lymphocytes and 15% monocytes. Numerous tests of the spinal fluid did not yield a diagnosis. At the end of two weeks, she spontaneously regained consciousness. One of the group of consultants who saw her suggested a course of Rocephin because one blood specimen showed antibodies against *Borrelia*. She was given 2 grams a day intravenously. There was no apparent response to this and she continued to have malaise, fatigue, and generalized weakness. In November of 1989, she developed optic neuritis in her left eye. When I saw her in November of 1989, her complaints were of lack of concentration, generalized joint pains and weakness of her right arm and leg. She was ataxic, had hyperactive reflexes, and absent abdominal reflexes. She was totally disabled from her profession and continued to be so when I last saw her in 1996.

Case 2

This female nurse was 38 years of age when she received a hepatitis B vaccination in July of 1988. Two weeks after the injection she developed generalized weakness, lethargy, and muscle pain. In September of 1988 she consulted a rheumatologist, who when he found that her antinuclear antibody titer was 500, started her on a high dose aspirin program. The aspirin helped her joints but she had to discontinue it because of gastric irritation.

During the next four years, she struggled with symptoms of joint pains and what we now call the "chronic fatigue syndrome". She received no help from Aralin that was prescribed for a presumptive diagnosis of lupus erythematosus.

In July of 1993, she suffered a seizure and went into a deep coma from which she could not be aroused. Her spinal fluid showed a "modest" number of mononuclear cells.

The coma lasted for three weeks and showed no sign of abating until she, at the suggestion of one of the numerous specialists who saw her, was given a series of plasmapheresis treatments. She rather quickly “came to” and became responsive. She had lost the vision in her left eye. She continued to improve under a vigorous physiotherapy program but was left with the chronic fatigue syndrome.

The coterie of physicians who saw her during the acute phase of her illness was not, even after multiple studies, able to come up with a definitive diagnosis.

In April of 1994, she saw Dr. Charles Poser, a professor of neurology at the Harvard Medical School in consultation. He suggested the diagnosis of post vaccinal encephalomyelitis.

I saw this patient in December 1994. She was blind in the left eye, had a staggering gait, and hyperreflexia except for absent abdominal reflexes. She had an antinuclear antibody titer of 1:320 and highly positive titers against Epstein-Barr and cytomegalovirus. She had all the criteria for the chronic fatigue syndrome.

When contacted in 1999 she stated that she still was chronically fatigued and blind in her left eye. She never had been able to go back to work. A lawsuit against the manufacturer of the vaccine for “failure to warn” had been settled out of court with the usual secrecy provision.

At this point in our knowledge, this woman suffered from multiple effects of a chronic autoimmune disease that followed her hepatitis B vaccination.^{71,72} Also manifest were post vaccinal encephalomyelitis and chronic fatigue syndrome of the type to be discussed later in this consilia.

Case 3

This male social worker was 32 years of age when he was vaccinated against hepatitis B virus in March, April and October of 1997. Past history revealed migraine headaches and moderate anxiety. He was functioning well on his job.

Shortly after the first injection, he experienced headaches, extreme fatigue, and generalized muscle and joint pain. These lasted for about ten days. After the second injection in April of 1997, he noted severe headaches, extreme lassitude and generalized aches and pains. Two weeks after this injection he had several short-lived “blackouts”.

Almost immediately after the third injection, he became withdrawn and listless. He went into a fugue state in which he was semiconscious and seemed confused. (His devoted mother supplied this part of the history.) This lasted for about a year when his parents found him disheveled and incoherent in a filthy apartment. They insisted that he move in with them.

In November of 1998, because of shortness of breath on exertion, and abnormal EKG and an abnormal echocardiogram, he consulted a cardiologist that made the diagnosis of idiopathic cardiac myopathy because of a low ejection fraction on an echocardiogram. The patient continued to live with his parents. He exhibited all the manifestations of the chronic fatigue syndrome.

In December of 1999 and in February of 2000 he was seen respectively, by me and by an internist in his home state. Our findings were essentially the same. My history was described above and the physical examination by both of us was unrevealing. An MRI was normal. The history reported to the other doctor was of chronic pain, extreme fatigue, blackouts, joint swelling, joint pains, episodes of incontinence, and paresthesia of his left arm.

Extensive laboratory studies showed autoantibodies against the myocardium, elevated Epstein-Barre virus antibodies, and low compliment levels. Studies for antinuclear antibodies, Lyme disease, hepatitis C, and AIDS were negative.

On September 20, 2001, he was seen in consultation by a professor of neurology at a major medical school. His report read, "On reviewing the clinical course, I believe he suffered an unusual immune mediated reaction to the hepatitis B vaccination. I have seen another similar patient and have obtained literature documenting similar cases."

Thus the three of us who have studied this man agree that he suffered acquired autoimmunity that followed hepatitis B vaccination.

C. Variants of the Chronic Fatigue Syndrome that have occurred after hepatitis B vaccination.

Dr. Claire Flemming, a British physician, in an article published in the British Medical Journal in 1992, graphically describes the chronic fatigue syndrome that she suffered from after receiving a hepatitis B vaccination.

Case 1

The previously well, successful, dynamic business man was in excellent health prior to his receiving a hepatitis B vaccination in June of 1997. He was 36 years old at that time. One week after the vaccination he became acutely ill with a severe headache, profound sweats, and generalized muscle and joint aches. A main feature of his distress was that he lost his intellectual sharpness and ability to concentrate. The headaches and muscle and joint pains abated somewhat. However, because of the mental acuity and fatigue aspects of his disease, he was forced to leave his financially responsible work.

During the 27-month interval between his vaccination and his examination in my office on September 14, 1999, he had suffered a symptom complex that included, in their order of causing difficulty, cognition and memory problems, bone pain, muscle pains, abdominal pain and chills. He intermittently, has a rash suggestive of either a viral

disease or leukocytoblastic vasculitis. He had some aphthous ulcers, which brought up the questions of Behcet's disease. He saw a specialist who discounted this possibility. On the advice of specialists at the medical center he went to, he empirically took prednisone, methotrexate, and the various non-steroidal anti-inflammatory medications. None of these appeared to help relieve his symptoms.

The history I obtained is detailed above. Extensive laboratory studies were reviewed and appeared to rule out any serious disease. The positive laboratory studies done in my clinic, revealed antibodies against Epstein-Barre, cytomegalovirus, and herpes 6 viruses. He also had thyroid peroxidase antibodies.

In July of 2001, he was contacted and there was no change in his condition. He remained totally disabled from his business profession.

I included this patient under the chronic fatigue syndrome section of this consilia because his clinical presentation, at this point, seems most like this syndrome.

Case 2

This professional woman had a medical history that was completely negative for any previous diseases received a hepatitis B vaccination in September and October of 1993, and February of 1994. At that time, she was 46 years old. Within several weeks after the third vaccination, she developed extreme fatigue and muscle pains. She consulted a rheumatologist who found an antinuclear antibody titer of 1:160. He found no stigmata of lupus erythematosus.

She had continued to be essentially disabled with extreme fatigue and muscle aches and pains until the time I saw her on April 16, 1998. She had been to numerous physicians since 1995, none of who came up with a definitive diagnosis. In addition to the positive ANA, the laboratory findings included high titers against the Epstein-Barr virus, the cytomegalovirus, herpes 6 virus, mycoplasma pneumoniae, and candida albicans. An MRI study was negative for multiple sclerosis. She had symptoms of fibromyalgia but did not have the specific pressure pain areas characteristic of the disease.

I saw this patient on six occasions between April 1998 and September 2000. I empirically gave her a course of Valtrex on the basis of her viral studies and a course of Aralin as an attempt to help her joint pains. Neither of these medications seemed to help her. When contacted in July 2001, she still stated that she was the same and was still disabled due to extensive fatigue, generalized joint pains, and mentation difficulties.

Case 3

This young girl was 14 years of age when she received a series of three hepatitis B vaccinations. Prior to that time, according to her and her parents, she had always been in "perfect health". Two hours after the first injection in August 1998, she developed

weakness, fever, chills, and headache. It took two weeks for these to subside. In September 1998, after a second vaccination, there was a repeat of the reactions but they were less severe. After the third vaccination in February of 1999, she again had the symptoms of chills, fever, and joint pain but they were less severe than when they occurred after the first two vaccinations.

Since that time, she developed severe, headaches, facial twitching, jaw pain, muscle cramps, chills, burning pains in her back, numbness in her legs, poor balance, mood swings, depression, and cognition difficulties. This amazing array of problems did not come all at once, but gradually came on to the time I saw her in August of 2000. Her previous excellent performance at school had dropped off to the extent that she was only going half time.

At the time of my examination, she had the clinical picture of the chronic fatigue syndrome with severe fatigue, somnolence during the day, weakness, muscle aches, and the inability to concentrate. Although it seemed on a temporal basis that she had an acquired autoimmunity reaction to the hepatitis B vaccination, I decided to treat her as I had been doing for people with the chronic fatigue syndrome. She was started on 5 cc. of gamma globulin weekly for four weeks then monthly. She was also given Valtrex 2 grams per day. She was slightly hypothyroid so she was given 2 grains of thyroid a day.

Over the next two years, there was gradual improvement. By July of 2001, she had resumed her normal activities and was performing her schoolwork at her usual standard. She was even playing volleyball. We will never know what caused her turn around but the fact remains that her difficulties started after her hepatitis B vaccination.

D. Guillain-Barre syndrome after a hepatitis B vaccination in a newborn infant.

This syndrome was the first complication of hepatitis B vaccine to be established.

This case report addresses the importance of recognizing the possibility that the hepatitis B vaccine can cause Guillain Barre Syndrome in a newborn. This recognition is important because treatments for this condition that might prevent permanent damage are available.

This report concerns a case of probable Guillain Barre Syndrome that followed a hepatitis B vaccination. It is suggested that if the probable cause of the syndrome had been recognized earlier the outcome may have been different.

Case report: The patient was a baby boy who had a full term uncomplicated delivery in May of 1995. The pregnancy had been free of complications as well. He appeared completely normal after delivery and at ten days of age received a routine hepatitis B vaccination. He continued to do well and was nursing without difficulty until two weeks after his birth when he became extremely irritable and restless. The character of his crying changed and he began to have difficulty in breast feeding. He began to cry and scream almost nonstop when he was not nursing or sleeping. This lasted for six days

and then stopped. He was seen by his pediatrician in mid-June with the thought that he was a colicky baby. At home the pitch of his cry changed and generalized poor muscle tone was noted. By 2 1/2 months of age he had to be bottle fed and was not gaining weight. In August of 1995 he was seen by a pediatric neurologist at a neurologic specialty clinic who made a diagnosis of "untreatable congenital muscle disease". By mid-October he was unable to swallow, aspirated, and became areflexic.

He was admitted to a pediatric intensive care unit where because of weakness of his respiratory muscles, he had to be intubated and put on a respirator which to this day (July 2000) is necessary. A muscle biopsy was done and sent to pathologists at a children's center in the northeast. It was reported as "non-diagnostic".

In mid-December 1995 he was airlifted to a clinic in the Midwest where a second muscle biopsy was done. This was read as "possible infantile inflammatory neuropathy". It had become necessary to feed him through a stomach tube and a working diagnosis of infantile inflammatory myopathy was made.

He was then airlifted to a hospital near his home. Three days after admission, he was started on prednisone and intravenous gamma globulin. He stayed there until the beginning of February 1996 with equivocal improvement. He remained on the respirator.

He was then airlifted to another mid-western clinic for further evaluation and another extensive workup where a tracheostomy was done. He was weaned from prednisone and a "wait and see" decision was made. It was at this hospital that, for the first time, a neurologist suggested the diagnosis of Guillain Barre Syndrome. This neurologist felt that all other causes of his clinical course had been ruled out by the extensive studies that had been done in the specialty clinics in which he had been seen. His muscle enzymes at that time were slightly elevated. His neurologists thought this was due to stopping the prednisone.

He was then transferred back to the hospital near his home. In March 1996, after he had been in hospitals for five months, he was discharged home where he was cared for by a devoted family. They were supported by occupational, physical and speech therapists. In the summer of 1997 he was given an 8-month course of methotrexate and prednisone with no improvement.

He remains on a respirator and has a gastroscopy tube. He has no head control, cannot sit unassisted, cannot roll over or lift any of his limbs against gravity. He is able to communicate with eye gaze, but due to the tracheostomy, is unable to speak. He has had excellent multi-disciplinary supportive care and is getting along as well as can be expected.

Extensive laboratory studies ordered by each of the pediatric neurologists who saw this child did not help them in regard to the diagnosis. The spinal fluid examinations did not show elevated proteins, but it is known that this finding in the Guillain Barre Syndrome may be transitory.

Discussion: There is no intent in this case report to prove that recombinant hepatitis B vaccine causes the Guillain Barre Syndrome. However, it is to point out that this possibility exists. The Guillain Barre Syndrome is well accepted as an acquired autoimmune disease that can occur after a vaccination. In fact, the first reported case from which the syndrome gets its name occurred after a vaccination. The fact that this syndrome can occur after a viral vaccination was shown by the swine flu vaccination program of 1976. Since hepatitis B infection itself can cause the Guillain Barre Syndrome, Zuckerman's warning in 1976 that hepatitis B vaccine might cause some of the autoimmune complications that are caused by the disease itself, seems to have been borne out in this case. It was strongly suggested by the vaccine post marketing study done in 1986 and by numerous reports of this occurrence in the Vaccine Adverse Events Reporting System (VAERS) that the hepatitis B vaccine can cause Guillain Barre Syndrome.

Experience with Guillain Barre syndrome suggests that it can manifest itself many days after the precipitating cause, so the two week incubation period seen here does not rule out this syndrome.

The treatment of "possibilities" in severe clinical situations in which the diagnosis is not apparent is well known to experienced physicians. In fact, late in the course of the case under discussion, methotrexate and prednisone were given on this basis.

Plasmapheresis and gamma globulin are two well accepted treatments for the Guillain Barre Syndrome and a case could be made that if they had been administered when the situation was getting out of control that the outcome might have been different. This is the reason that the author feels it worthwhile to remind clinicians that treatable Guillain Barre Syndrome may occur after a hepatitis B vaccination and that recognized treatments for this syndrome are available.